

REVIEW ARTICLE

Cardiac Alternans: Diverse Mechanisms and Clinical Manifestations

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Objectives. The purpose of this review is to assemble the widely dispersed information about cardiac alternans and to categorize the types and mechanisms of alternans, their clinical manifestations and possible therapeutic implications.

Background. The phenomena of mechanical and electrical alternans have been of continuing interest to both physiologists and clinicians. Recent studies have enhanced this interest because of the reported association of alternans with experimental myocardial ischemia and cardiac arrhythmias.

Methods. The review formulates concepts based on extensive review of published studies and personal observations.

Results. Cardiac alternans has been subdivided into the following four categories: 1) mechanical, 2) electrical, 3) in association with myocardial ischemia, and 4) in association with cardiac motion. Mechanical alternans can be explained by hemodynamic or inotropic alterations, or both. Mechanical alternans in the ventricular muscle is accompanied by alternans of action potential shape. In the Purkinje fibers, action potential duration alternates

without change in shape and is determined by the duration of the preceding diastolic interval. However, in ventricular muscle fiber, alternans can occur in the presence of constant diastolic intervals. T wave alternans reflects changes in action potential duration and is frequently associated with a long QT interval. Electrocardiographic manifestations of conduction alternans occur at many different sites within the conducting system and myocardium. During myocardial ischemia, additional mechanisms of repolarization alternans have been proposed. Alternans occurring in the presence of a large pericardial effusion is attributed to swinging motion of the heart maintaining two-beat periodicity.

Conclusions. Since its origin as "pulsus alternans" described by Traube in 1872, the definition of alternans has evolved into a term encompassing multiple physiologic and pathologic phenomena that, although united by the term cardiac alternans, diverge widely with respect to etiology, mechanism and clinical significance.

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Since the first report by Traube (1) in 1872 of pulsus alternans, a condition characterized by alternation between a strong and a weak heartbeat during regular rhythm, the phenomena of mechanical and electrical alternans have been of continuing interest to both physiologists and clinicians. Recent studies have enhanced this interest because of the reported association of alternans with experimental myocardial ischemia (2,3) and cardiac arrhythmias (4). In addition, application of signal averaging and computer processing of the electrocardiogram (ECG) has revealed subtle forms of electrical alternans that may not be detectable by visual inspection (5), further increasing awareness of the frequency and possible physiologic significance of alternans. Diverse mechanisms for both electrical and mechanical alternans have been proposed.

Information on different forms of alternans is widely dispersed throughout the basic science and clinical literature, making an understanding of the scope of the phenomenon and the development of unifying concepts relative to its mechanisms and significance difficult to achieve. It is the

purpose of this study to facilitate this process by reviewing the published reports addressing the mechanisms and forms of cardiac alternans, their clinical manifestations and possible therapeutic and prognostic implications. The presentation follows the format outlined in Table 1. The discussion is confined to alternation of single mechanical or electrical events, or both, and does not include more complex forms, such as alternans at several levels of atrioventricular (AV) conduction in the anterograde (6,7) or retrograde (8) direction, alternans of Wenckebach periodicity (9,10), alternating coupling intervals of ventricular premature complexes (11) and alternating amplitude of afterdepolarizations (12).

Mechanical Alternans

In 1910, Thomas Lewis (13) concluded that cardiac alternans occurs under two circumstances: 1) in a normal heart as a result of marked acceleration of rate, and 2) in a heart with impaired or intoxicated heart muscle. Lewis (13) also showed that mechanical alternans can occur with or without concomitant electrical alternans. Other early observations on mechanical alternans were provided by Paul Dudley White (14), who, in 1915, observed alternans in patients with heart failure.

The mechanisms of mechanical alternans have been disputed. Wenckebach (15) proposed that pulsus alternans is a manifestation of concomitant alternations of end-diastolic

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Table 1. Types of Cardiac Alternans

Mechanical
Due to alternans of hemodynamic variables
Due to alternans of contractile state
Interrelation between mechanical and action potential alternans
Electrical
Alternans of action potential shape and duration
Electrocardiographic manifestation
Alternans of repolarization and refractoriness
Alternans of conduction
In association with myocardial ischemia
In association with cardiac motion

pressure and volume. Straub (16) postulated that the weak beat originated from a smaller end-diastolic volume but higher pressure and could be attributed to incomplete metabolic recovery. Wiggers (17) ascribed the phenomenon to alternation of the inotropic state. Subsequent studies, as discussed later, have validated both the hemodynamic and the inotropic hypotheses of mechanical alternans by demonstrating that mechanical alternans can result from alternation of hemodynamic variables such as pressure and volume or from alternation of inotropic state, or both.

Alternans of hemodynamic variables. Figure 1 from a study by McGaughey et al. (18) shows an example of pressure-volume relation during alternans in isolated perfused dog ventricle ejecting into a simulated aortic impedance. In this case, as a consequence of the Frank-Starling mechanism, stroke volume and systolic pressure are greater when end-diastolic volume is increased. Consequently, the heart empties more completely, which in turn results in lower end-diastolic volume, smaller stroke volume, lower systolic pressure and less complete ventricular emptying.

Figure 1. Pressure-volume plot of a weak (1) and a strong (2) beat of pulsus alternans during constant filling pressure in isolated cross-perfused dog heart. For explanation, see text. Reprinted, with permission, from McGaughey et al. (18).

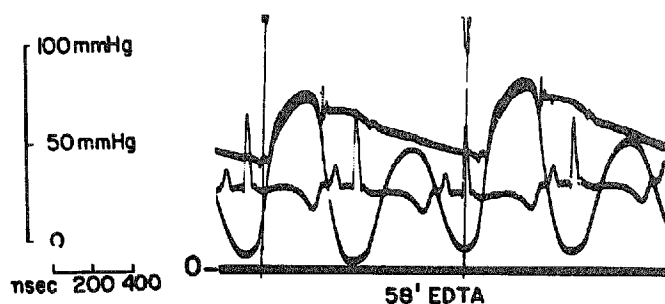
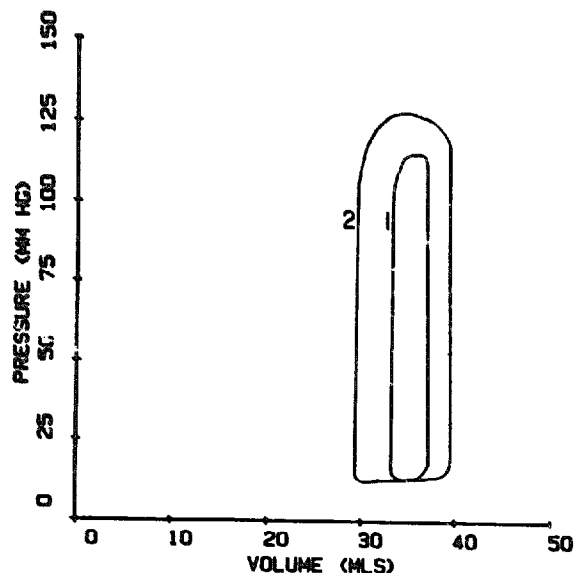


Figure 2. Ventricular pressure, aortic pressure and electrocardiogram from an open chest anesthetized dog during perfusion with disodium ethylenediaminetetra-acetate (EDTA) solution. The tracing shows pressure alternans without electrical alternans. Note that the second beat originates from a lower diastolic pressure than the first beat and the fourth beat from a slightly lower diastolic pressure than the third beat. Reprinted, with permission, from Surawicz (20).

The result is an increased diastolic volume and thus the continuation of alternans. Contributing to the maintenance of alternans induced by this mechanism is the longer duration of systole associated with the more forceful beat and thus less time for diastolic filling (19).

Figure 2, from a study by Surawicz (20), shows alternans of left ventricular pressure in an open chest dog with depressed myocardial contractility induced by hypocalcemia. It can be seen that higher systolic pressure originates from higher end-diastolic pressure. Other studies (21) demonstrated that in the dog heart in situ, the weak beat nearly always originated from a lower left ventricular end-diastolic pressure. Investigations by Mitchell et al. (22) in isolated supported dog hearts, dog hearts in situ and papillary muscle have shown, however, that weak beats can be initiated from a lower, the same or a higher end-diastolic pressure, but the weak beat in these preparations consistently originated from a shorter end-diastolic length of the contractile element. This condition can be brought about by an inadequate diastolic ventricular relaxation period or inadequate filling relative to the inflow volume required to produce any given diastolic fiber length from any given end-systolic volume, or both (22).

Other observations on hemodynamic alternans suggest that in the intact dog heart, the magnitude of alternans may be unequal in the two ventricles (23). Such discordant alternans in the dog heart has been attributed to changes in the initial segment length (24). In the human heart, alternans in the right and left ventricles can be concordant or discordant as shown by simultaneously recorded right ventricular and systemic arterial pressures (25).

Alternans of inotropic state. Nayler and Robertson (26) attributed mechanical alternans in dog papillary muscle to alternans of the contractile state because the alternans occurred without any change in end-diastolic tension. Subsequently, Noble and Nutter (27) demonstrated alternans in the absence of differences in diastolic filling duration.

Figure 3 from the study of McGaughey et al. (18) shows

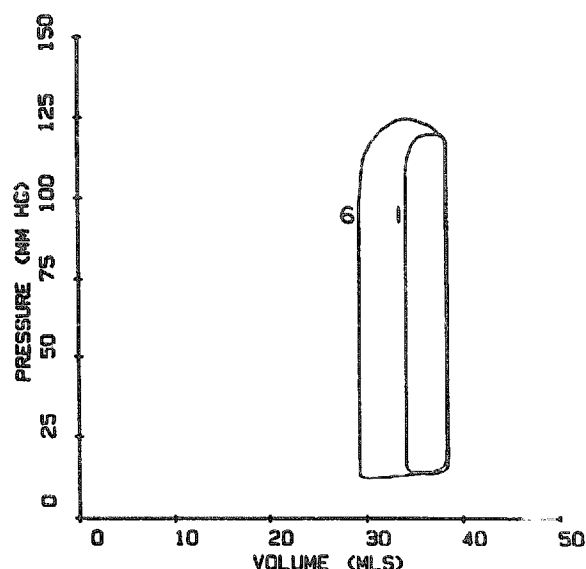


Figure 3. Pressure-volume plot of a weak (1) and a strong (6) beat of pulsus alternans during constant filling pressure in an isolated cross-perfused dog heart. For explanation, see text. Reprinted, with permission, from McGaughey et al. (18).

that unlike the relation illustrated in Figure 1, the diastolic pressure-volume relation does not differ significantly between the strong and the weak beat. This excludes incomplete relaxation, or the Frank-Starling mechanism, as the only cause of alternans. The authors (18) concluded that the magnitude of stroke volume alternation reflected the complex interactions of altered contractility state with alternation in preload and afterload. This view is in agreement with a computer model of alternans that also suggested interdependent changes in contractility and hemodynamics during alternans (28). In another study (29) in an intact blood-perfused pig heart preparation, the slope of the end-systolic pressure-diameter relation, which provides an index of contractility independent of end-diastolic diameter, was nearly two times greater in the strong than in the weak beat. Similarly, alternation of contractile state has been postulated in patients with aortic valve disease with an alternating maximal rate of left ventricular pressure increase (30,31) or alternating stress-length relation (32).

Experimental and clinical conditions for mechanical alternans. In the laboratory, alternans can be induced in normal hearts or isolated cardiac tissues by a variety of methods, of which the most frequently employed is a sudden increase in heart rate (33-38) or proper timing of a premature stimulus (19). Other methods have included hypothermia (34,39), application of metabolic inhibitors (40), lowering of extracellular calcium concentration (20,34,35,41), limiting oxygen availability (42) and the administration of various drugs (34,36,41).

Mechanical alternans in humans is typically associated with severe heart disease or heart failure, or both (14,43-45). Some of the recorded manifestations of mechanical alternans have included alternations of left ventricular systolic pres-

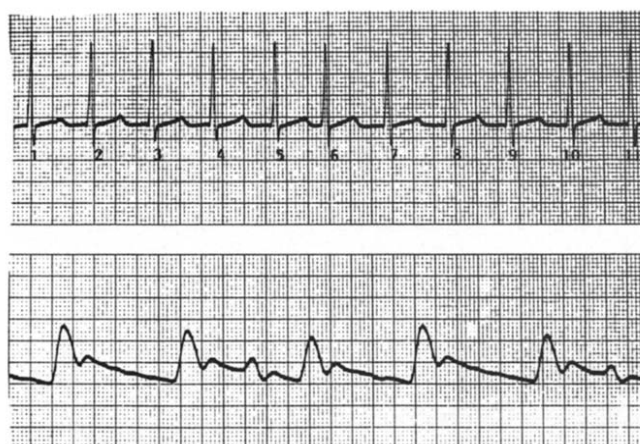


Figure 4. Alternans of aortic pressure in a patient on the first day after surgical aortic valve replacement. Note that the aortic valve does not open after the second, the sixth (premature) and the eighth complex. The electrocardiogram shows no alternans.

sure (46); left ventricular end-diastolic pressure (44,46); left ventricular end-diastolic volume (47); left ventricular end-systolic volume (48); stroke volume (46-48); duration of left ventricular ejection (44); peak aortic blood flow (44); right and left ventricular blood flow velocity (49,50); systolic and diastolic time intervals (51); left ventricular relaxation properties (52); right ventricular or pulmonary artery pressure, or both (53-56); and echocardiographic wall motion, valve dynamics and dimensions (57-62). Verheugt et al. (63) described two unusual cases of pulsus alternans caused by an alternating atrial electromechanical dissociation manifested by *a* wave alternans.

Interrelation between mechanical alternans and action potential alternans. Mechanical alternans has been recorded in the absence of electrical alternans in isolated papillary muscle (26,34). In addition, there are numerous examples of mechanical alternans in the absence of alternating configuration of the ECG complexes in animals (Fig. 2) and humans (53-65) (Fig. 4).

At the cellular level, mechanical alternans in ventricular myocardium is usually accompanied by an alternating shape of the ventricular action potential. Alternans of action potential shape has been designated as discordant when a stronger beat is associated with a shorter plateau of the ventricular action potential (that is, a more triangular shape) and the weaker beat with an action potential having a longer plateau (that is, a more square shape) (34,66-68). When mechanical alternans results from alternating excitation failure of regional contractile units, the records may also show alternating absence of action potentials at selected recording sites (34).

The concomitant occurrence of action potential shape and muscle tension alternans can result from one of the following processes: 1) action potential shape determines the developed tension; 2) developed tension determines the action potential shape; and 3) both action potential shape

and tension change independently but perhaps because of a common factor. The first possibility appears unlikely. If the currents generated during repolarization contributed to a positive inotropic effect, the developed tension should be greater in association with a longer plateau and a more positive plateau potential. However, this was not the case (37). Similarly, if alternans of action potential shape was caused by passive mechanoelectrical coupling (69), we would expect a positive correlation between the developed tension and the amplitude of alternans. However, in the study of Saitoh et al. (37), this was not the case. Therefore, it is most likely that action potential shape and tension are modulated by a common factor.

The factor common to both action potential and mechanical alternans may be a defect in calcium utilization (36,41). In a study by Orchard et al. (70) in ferret papillary muscles and isolated myocytes, stronger contractions during mechanical alternans were associated with longer action potential, and alternans paralleled alternations of calcium-activated inward current. The mechanical alternans in isolated myocytes persisted when the electrical alternans was prevented by voltage-clamped depolarizing current pulses of constant duration (70). This observation suggested to the investigators that action potential alternans is caused by an alternating magnitude of the calcium transient. Oscillations of intracellular calcium transient concomitant with oscillation of contractile force have been reported in rat and rabbit (71) and in ferret (70,72,73) ventricular muscle. Also, alternation of the calcium transient has been recorded during mechanical and electrical alternans in the setting of myocardial ischemia (74). Lab and Lee (73) have shown that such alteration of intracellular calcium occurred in the presence of complete relaxation.

It has been shown that alternans in ventricular muscle fibers was not altered by either doubling or decreasing by 50% the extracellular calcium concentration and by increasing the sensitivity of contractile proteins to the action of calcium; however, alternans was suppressed or markedly attenuated by caffeine and ryanodine (75). Because both caffeine and ryanodine abolish the oscillations of the intracellular calcium transient and of tension in calcium-overloaded ferret ventricular muscle, it appears that suppression of alternans may be caused by lessening fluctuations of the amounts of calcium released by sarcoplasmic reticulum. However, this may not be the only mechanism of alternans suppression because alternans is also attenuated or suppressed by the calcium channel activator Bay K 8644 (37) and calcium channel blockers (37,76), presumably as a result of changing amounts of calcium entering through sarcolemmal calcium channels. Furthermore, it has been shown (37) that neither the maintenance nor the suppression of alternans is dependent on any particular level of developed tension or plateau duration. Thus, alternans may be suppressed or attenuated when the duration of plateau is increased or decreased and in the presence of both decreased and increased tension.

Electrical Alternans

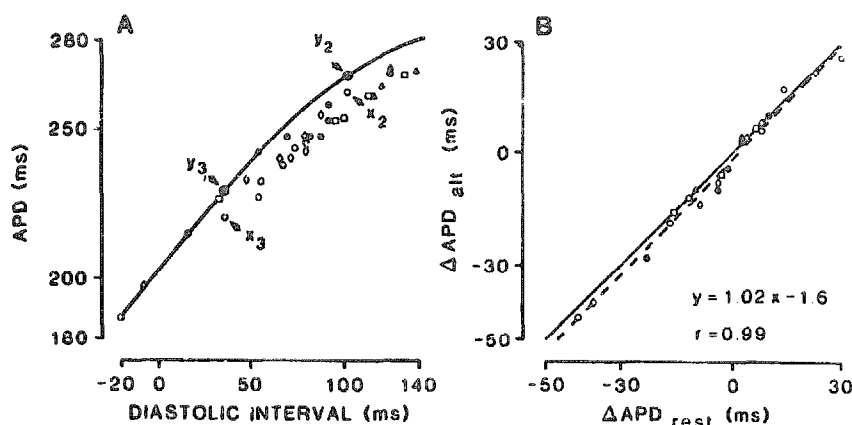
Action potential alternans in Purkinje and ventricular muscle fibers: similarities and differences. In Purkinje fibers, action potential duration changes during alternans occur without changes in action potential shape. In ventricular muscle fibers, action potential duration changes are accompanied by changes in action potential shape, but alternans of action potential shape may be present when the diastolic intervals are constant (37,68,77). Several studies (34-36,77) have shown a lack of consistent relation between the duration and shape of action potentials in ventricular muscle fibers. For example, when alternans was induced by a sudden increase in the rate of stimulation in dog ventricular muscle, the first action potential with a square configuration was longer than the following triangular action potential, but subsequently the triangular action potentials were usually longer than the square ones when measured both at the end and at the -60 -mV level of repolarization (37).

There is evidence that for both normal Purkinje and ventricular muscle fibers under physiologic conditions a critical short cycle is required for induction of alternans and, in both, the magnitude and duration of alternans increase with shortening of the new cycle length (37,41). However, no such requirements appear to be necessary when alternans is induced by interventions that alter metabolic state, such as the application of triiodothyronine, 2,4 dinitrophenol, anoxia (78), quinidine, a combination of low temperature and propranolol (77) or low temperature alone.

Alternans of action potential duration induced by a sudden decrease in cycle length could be explained by the mechanisms that control action potential duration during nonsteady states in the absence of alternans (that is, restitution and memory) (79,80). Figure 5 illustrates the close correlation between action potential duration during restitution and during alternans in canine Purkinje fiber (37). The distribution of action potential durations during alternans parallels the course of restitution (Fig. 5A) but because of declining memory effect, the action potentials during alternans are shorter than those during restitution at each of the corresponding diastolic intervals. The closeness of correlation is revealed when the difference between two consecutive action potential durations during alternans is plotted against the corresponding difference between two action potential durations during restitution at common diastolic intervals (Fig. 5B).

Figure 6 shows the relation between action potential duration during restitution and during alternans in canine ventricular muscle fibers (37). Unlike in Purkinje fibers (Fig. 5), the distribution of action potential durations during alternans does not parallel the course of restitution (Fig. 6A). Figure 6B shows that there is no correlation when the difference between two consecutive action potential durations during alternans is plotted against the corresponding differences between two action potential durations during

Figure 5. A, Relation between action potential duration (APD) (ordinate and diastolic interval) (abscissa) during electrical restitution (solid line) and alternans (scattered symbols) in canine Purkinje fibers. Alternans was induced by abrupt change from a cycle length of 1,000 ms to four shorter cycles. Δ = first to fourth action potential after changing cycle length to 360 ms; \bullet = first to seventh action potential after changing cycle length to 340 ms; \diamond = first to eighth action potential after changing cycle length to 320 and 300 ms, respectively; X_2 and X_3 = durations of second and third action potential at a cycle length of 300 ms, respectively; Y_2 and Y_3 = corresponding action potential durations on the restitution curve at common diastolic intervals with X_2 and X_3 . B, The difference between two consecutive action potential durations during alternans (ΔAPD_{alt}) is plotted against the corresponding difference between two action potential durations on the restitution curve at the common diastolic interval (ΔAPD_{rest}) for 22 pairs of consecutive action potentials from Figure 2A. Solid line = identity line; interrupted line = fitted to data by linear regression. Reprinted, with permission, from Saitoh et al. (37).



restitution at common diastolic intervals for 30 pairs of consecutive action potentials from Figure 6A.

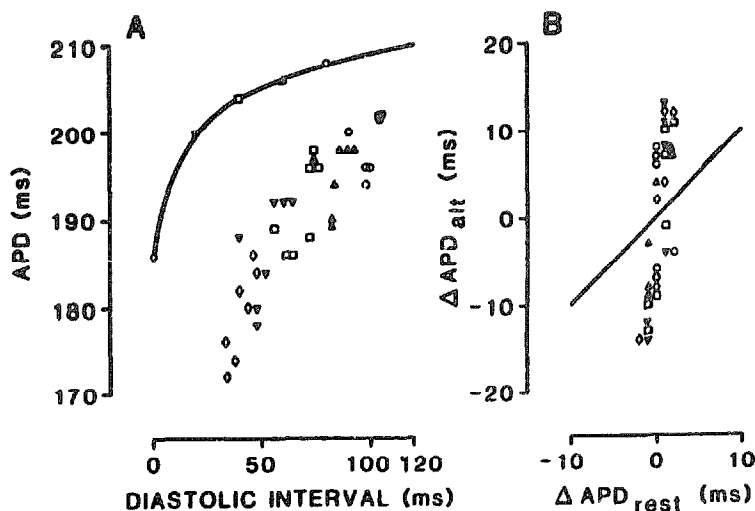
Figures 7 and 8 show concomitant action potential and contraction alternans in isolated perfused rabbit heart in the presence of quinidine (Fig. 7) and at low temperature (Fig. 8). In both Figures 7 and 8, the diastolic intervals preceding the alternating triangular and square action potentials are nearly equal, which suggests a mechanism not dependent on the differences of the preceding diastolic intervals.

It has been shown (37) that in Purkinje fibers, alternans induced by an increase in cycle length always declined progressively and disappeared before the action potential duration reached the new steady state. Also, in Purkinje fibers, alternans could be interrupted at any time by interpolating an interval in which the sum of the preceding

diastolic interval and the following action potential duration did equal the cycle length (37). In ventricular muscle fibers, the magnitude of alternans induced by a decrease in cycle length also tended to decrease progressively because of declining memory effect. However, at very rapid rates, alternans of action potential shape in ventricular muscle fibers could continue indefinitely without a change in diastolic interval. In ventricular muscle fibers, alternans of action potential duration could be interrupted by interpolating a single cycle, but unlike Purkinje fibers, the sum of the preceding diastolic interval and the following action potential duration of the cycle interrupting the alternans did not have to equal the cycle length (37).

The observed differences between action potential alternans in Purkinje and ventricular muscle fibers can be attrib-

Figure 6. Alternans of action potential duration (APD) in dog ventricular papillary muscle fibers induced by an abrupt change from a cycle length of 1,000 ms to shorter cycle lengths. A, Relation between action potential duration (shown on the ordinate and the preceding diastolic interval (DI) shown on the abscissa) during electrical restitution (solid line) and alternans (scattered symbols) in a canine ventricular muscle fiber. \circ , Δ , \square , ∇ , \diamond = first to eighth action potentials after changing cycle length from 1,000 to 300, 280, 260, 240 and 220 ms, respectively. B, The difference between two consecutive action potential durations during alternans (ΔAPD_{alt}) is plotted against the corresponding difference between two action potential durations on the restitution curve at the common diastolic interval (ΔAPD_{rest}) for 30 pairs of consecutive action potentials from A. Solid line = identity line. Reprinted, with permission, from Saitoh et al. (37).



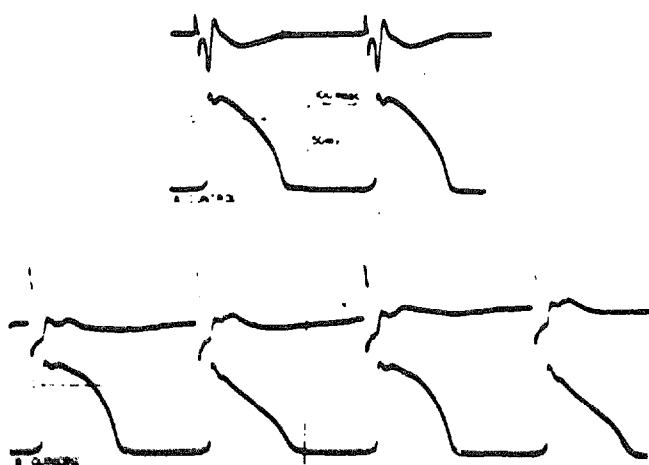


Figure 7. Paced electrocardiogram and ventricular action potential in isolated perfused rabbit heart before (top) and after (bottom) treatment with quinidine. Note alternans of T wave and action potential shape in the presence of a nearly identical diastolic interval before the square and triangular action potentials. For interpretation, see text. Reproduced, with permission, from Zumino A, Surawicz B. Unpublished data.

uted to the presence of a single mechanism in Purkinje fibers and more than one mechanism in ventricular muscle fibers. In Purkinje fibers, changes in action potential duration are controlled by the duration of the preceding diastolic interval. This has been attributed to the effect of the decaying delayed outward-rectifying potassium current causing greater action potential shortening after a short than after a long diastolic interval (81). A similar mechanism, although caused by different plateau currents from those in Purkinje fibers, has been proposed for action potential alternans of ventricular muscle fibers (79). However, as discussed earlier, additional mechanisms have been postulated to explain alternans of action potential shape in the ventricular myocardium associated with alternans of intracellular calcium transients and developed tension.

Atrial alternans. In two published reports (82,83) of atrial action potential alternans, action potential duration was dependent on the preceding diastolic interval. However, the mechanisms differed. In strips of normal canine atrial tissue, induction of alternans required a critical increase in stimulation frequency (83). In human patients with heart disease, alternans of monophasic action potential duration was attributed to tissue damage, rather than to a critical increase in heart rate (82).

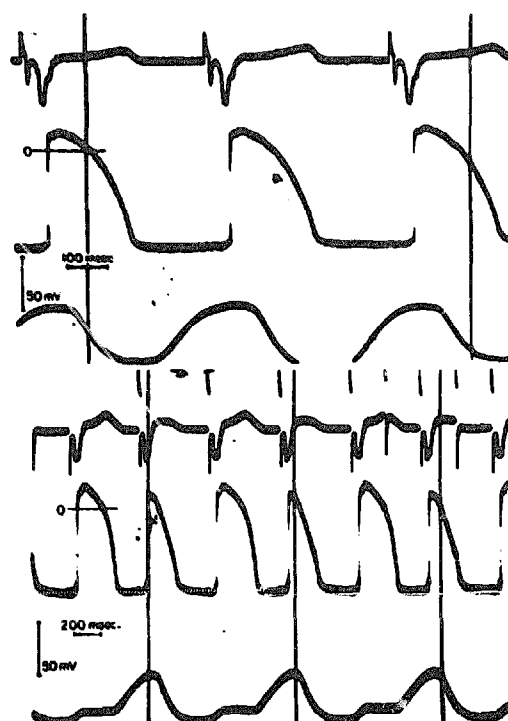
Electrocardiographic Manifestations

In 1950, Lepschkin (84) proposed classifying ECG manifestations of electrical alternans into the following categories: 1) alternating conduction delay; 2) primary alternation of the ST segment; 3) regression of restitution of the steady state, "resulting in primary T wave alternans"; 4) electrical alternans secondary to mechanical alternans; and 5) various

combinations of the four mechanisms. Although Lepschkin's concepts have been modified and refined with advances in cellular and subcellular cardiac electrophysiology, they continue to be essentially correct. The following discussion will group ECG manifestations into 1) repolarization alternans, and 2) conduction and refractoriness alternans. Alternans during myocardial ischemia and alternans due to cardiac motion will be discussed in separate sections.

Ventricular repolarization alternans: T wave, U wave and QT interval. In clinical electrocardiography, ventricular repolarization alternans is most frequently associated with abrupt changes in heart rate (85) or prolongation of the QT interval. Alternans of the T wave is the consequence of alternating the duration or shape, or both, of the ventricular action potential. It may be expected to occur when the diastolic interval becomes sufficiently brief to produce measurable shortening of the following action potential, which in turn will lengthen the subsequent diastolic interval and perpetuate the continuation of alternation (Fig. 9). When alternans is initiated by such a mechanism, the duration of the QT interval determines the critical cycle length at which alternans of ventricular repolarization may be expected to appear. The longer the QT interval, the longer the shortest cycle length at which alternans can occur. When the QT interval is prolonged, the T wave tends to encroach on the U

Figure 8. Electrocardiogram (top), ventricular action potential (middle) and contraction (bottom) in isolated perfused rabbit heart at 37°C (A) and 26°C (B). The heart is paced in both A and B, but the paper speed is different. Note alternans of T wave, action potential shape and duration and contraction at low temperature. Stronger contraction (downward deflection) is associated with a shorter triangular action potential. Reproduced, with permission, from Zumino A, Surawicz B. Unpublished data.



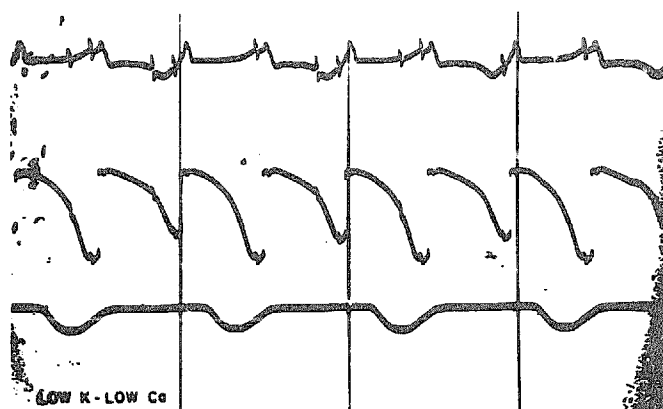


Figure 9. Example of alternans dependent on the alternans of the preceding diastolic interval. Alternans of repolarization in the electrocardiogram (upper trace) and ventricular transmembrane action potential (middle trace) in paced isolated rabbit heart perfused with a potassium- and calcium-deficient solution. Note that the shorter action potential takes off during incomplete repolarization of the preceding action potential and is followed by a distinct diastolic interval at the level of resting membrane potential. For interpretation, see text. Reproduced, with permission, from Zumino A, Surawicz B. Unpublished data.

wave, resulting in fusion between the two waves. Under such circumstances, alternans has been described as U alternans (86) or QU alternans (87,88).

A prolonged QT interval not only predisposes to T wave alternans but also frequently reflects the presence of an electrophysiologic substrate generating a polymorphic ventricular tachycardia known as torsade de pointes (39). Therefore, it is not surprising that T wave alternans has been implicated as a precursor of torsade de pointes (90). However, this association may be only a fortuitous result of a common electrophysiologic abnormality. Alternans of the T wave that is dependent on critical shortening of the diastolic interval frequently becomes manifest when the duration of ventricular action potential approaches or exceeds the cycle length (Fig. 9) (91). Therefore, a QT interval occupying nearly the entire cycle length can be seen in many cases illustrated in published reports of repolarization alternans associated with a long QT interval. Thus, it may be assumed that a long QT interval reflects an electrophysiologic abnormality that precipitates both repolarization alternans and torsade de pointes.

In experimental animals, T wave alternans can be induced by lowering the serum calcium concentration (92,93). In humans, T wave alternans associated with a long QT interval has been reported in congenital long QT syndrome (94-96), hypocalcemia (97), treatment with quinidine (98), hypokalemia (99), hypokalemia with hypocalcemia and hypo-

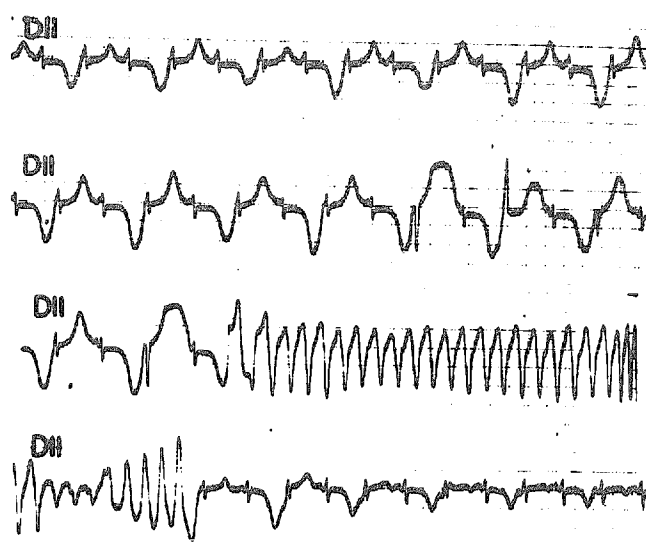


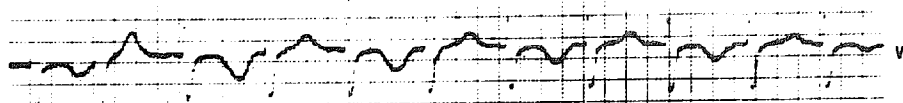
Figure 11. Electrocardiogram (continuous tracing) from a deaf-mute patient with familial long QT syndrome. Note T and QT alternans before and after a short episode of ventricular tachycardia. Reprinted, with permission, from Pernot C, Henry M, Debrulle C. Les syndromes cardio-auditifs d'origine genetique. *Coeur Med Int* 1974; 13:429-43.

magnesemia (86) and cardiomyopathy associated with hypomagnesemia (100-102) after defibrillation (103). Its occurrence has also been unexplained (104). Examples of T wave alternans associated with a long QT interval are shown in Figures 10 and 11.

In addition to manifest alternans in the clinical ECG, subtle alternans forms may become detectable by digital processing techniques (5). It has been shown (4) that such subtle forms of alternans are associated with a decreased ventricular fibrillation threshold in dogs and increased susceptibility to inducible ventricular tachycardia and ventricular fibrillation in patients with coronary artery disease or cardiomyopathy and therefore may represent a noninvasive marker of electrical instability. It has been suggested that the decreased ventricular fibrillation threshold in dogs with T wave alternans may be due to increased dispersion of repolarization (105).

Alternans of action potential duration is probably responsible for alternans of refractory periods. Janse et al. (106) recorded transient alternans of effective refractory periods after a sudden increase in heart rate in dogs. In humans, transient alternans of variable duration has been recorded both in the ventricular myocardium and in the conducting system during rapid stimulation or after a premature stimulus (107-109). Two examples are shown in Figure 12.

Figure 10. T wave alternans initiated by a premature impulse. Note the gradually decreasing magnitude of T wave alternans.



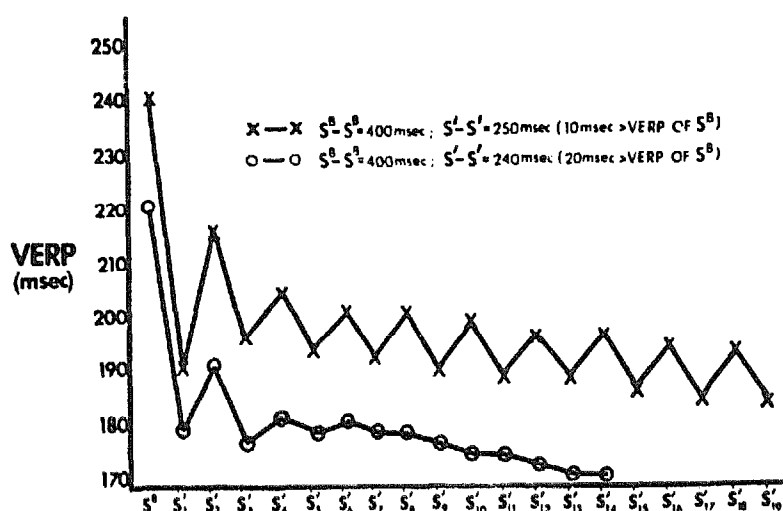


Figure 12. Effect of an abrupt change in cycle length from basic cycle (S^B-S^B) to a shorter cycle ($S-S$) on ventricular myocardial refractoriness (VERP) in two different experiments in humans. Upper curve shows persistence of alternans for the duration of the new cycle length ($X-X$); lower curve depicts rapid dampening of oscillations ($O-O$). Consecutive beats on the abscissa are marked from S^B to S_{19}^B . Reprinted, with permission, from Marchlinski (109).

Alternans of conduction. Conduction alternans may be due to alternation of one or more of the following determinants of impulse propagation: conduction velocity, refractoriness, excitability, supernormality and propagation pathway. Factors precipitating alternans include such variables as changes in heart rate, prematurity and various hemodynamic, nervous, humoral and pharmacologic inputs. Both the underlying mechanism and the precipitating factors may be difficult to identify.

In the surface ECG, alternans of conduction may manifest as 1) alternating duration or morphology, or both, of the P wave or QRS complex, or both; 2) alternans of the PR or RP interval; 3) alternans of the cycle length; and 4) various combinations of these. The diagnosis of alternans manifested by an alternating cycle length requires documentation of regular impulse formation at a fixed site of origin. Table 2 lists structures that may be involved in conduction alternans.

Atria. Rapid atrial pacing may result in alternans of atrial electrograms (110,111), but P wave alternans is rarely recorded in humans (112) (Fig. 13A) and, when present, it is usually accompanied by alternans of the QRS complex, ST segment and T wave, the so-called total alternans (113). Alternans of atrial flutter waves (114) as well as of the PP

interval during rapid heart rates, such as atrial tachycardia, have been recorded (Fig. 13C) (111,113).

Atrioventricular junction. Alternation of AV conduction in anterograde and retrograde directions has been recorded at normal and rapid heart rates (Fig. 13B), frequently with rapid pacing (113). Alternans of AV or ventriculoatrial conduction can be accompanied by QRS alternans or cycle length alternans.

Since 1925 when Lewis (115) first described AV node alternans, several mechanisms have been proposed to explain this phenomenon (116), including 1) conduction during the supernormal phase of recovery (117,118); 2) concealed AV conduction of atrial premature impulses, lengthening the

Figure 13. A, Sinus rhythm with alternans of the P wave. B, Sinus rhythm with alternans of the PR interval, most likely due to dual atrioventricular (AV) node conduction. C, Atrial tachycardia with 2:1 AV block, with alternation of the PP interval with the shorter PP interval encompassing the QRS complex. A disturbance of conduction or excitability at or near the site of regular impulse formation is postulated. However, an irregular impulse formation such as a ventriculophasic arrhythmia cannot be ruled out, making it uncertain whether this is a true conduction alternans. L = lead; M = monitor lead.

Table 2. Anatomic Structures Involved in Conduction Alternans

Atria
AV junction
Bundle branches
Single
Both
Fascicles
Distal Purkinje fibers
Ventricular myocardium
Accessory AV pathway
Alone
With AV junction
Various combinations of the above

AV = atrioventricular.

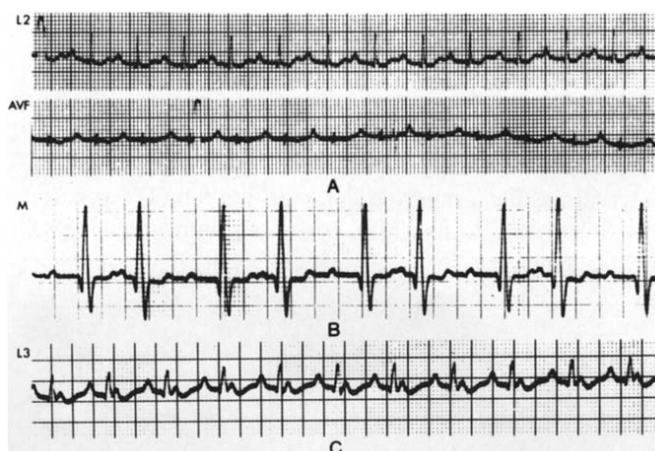
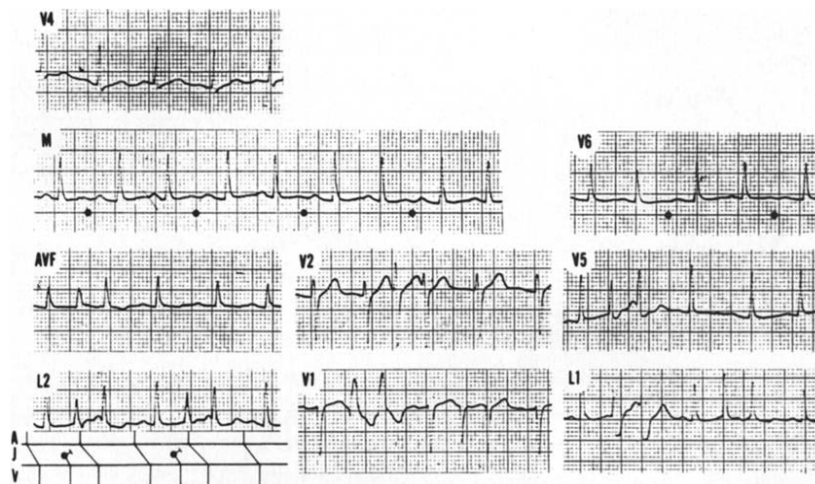


Figure 14. Example of PR alternans caused by concealed atrioventricular junctional (AVJ) discharge. Sinus rhythm with a normal PR interval is recorded in lead V₄ (the control lead). The PR and RR alternans are recorded in leads M (monitor) and V₆. The PR interval alternates between 0.16 and 0.22 s. In lead aVF, an interpolated AVJ premature complex is followed by PR alternans. The RR interval encompassing the interpolated AVJ premature complex is the same as the longer RR intervals in leads M and V₆. The shorter RR intervals encompass a PR interval of 0.16 s and the longer RR interval a PR interval of 0.22 s. The prolongation of the PR interval is the result of concealed AVJ discharge (solid circles). The same sequence of events is recorded in leads V₂ and V₅. Manifest AVJ trigeminy, with or without aberration, is recorded in leads II (L2), V₁ and I (L1) (bottom row). The analysis is aided with the Lewis diagram.



The RR intervals encompassing the manifest AVJ complexes, being equal to the RR cycles encompassing the prolonged PR interval but without manifest AVJ impulses, support concealed AVJ discharge as the mechanism of the PR alternans. The prolonged PR intervals, whether or not preceded by a manifest interpolated AVJ premature complex, are the same in duration, lending further support to concealed discharge as the mechanism of the PR alternans. Reprinted, with permission, from Fisch C. Concealed conduction. In: Zipes D, ed. Cardiology Clinics. Symposium on Arrhythmias I. Philadelphia: WB Saunders, 1983:63.

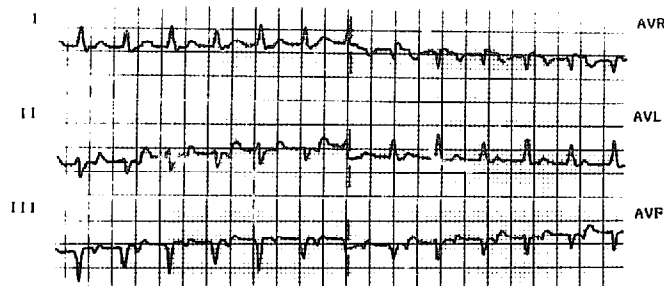
subsequent PR interval; 3) concealed AV junctional impulses with prolongation of the subsequent PR interval (Fig. 14); and 4) alternation of conduction between two functionally separate AV node pathways (Fig. 13B and 15) (119,120). In Figure 13B, alternans of the PR interval is most likely due to dual AV node pathways (113). The alternans of the PP, PR and RR intervals in Figure 15 (assuming regular impulse formation at a single site) can be explained by one of the following mechanisms: 1) AV junctional tachycardia with 3:2 type I anterograde and retrograde block; 2) atrial tachycardia with 3:2 exit block and a dual AV node pathway responsible for PR alternans; and 3) reentrant AV node tachycardia with

a single retrograde pathway and two anterograde pathways with different conducting properties (113).

Bundle branches. Alternation of either right or left bundle branch block with normal conduction, as a rule referred to as 2:1 bundle branch block (113), may be tachycardia- or bradycardia-dependent (121). Although the mechanism is not always clear, it has been suggested that every second impulse conducts during the supernormal period of recovery of excitability. Others (121) proposed that alternating cycle length differences result from transseptal retrograde penetration of the affected bundle branch.

Figure 16 shows different types of bundle branch block alternans. Alternation of complete right and left bundle branch block conduction during normal sinus rhythm is rare (Fig. 16E). Even rarer is alternation of complete and incomplete bundle branch block (Fig. 16D) or a combination of PR alternans with simultaneous bundle branch block alternans (Fig. 16F). Alternating conduction along the left anterior and posterior fascicles is most often accompanied by an incomplete or complete right bundle branch block and represents one type of bidirectional ventricular tachycardia (Fig. 17). It may occasionally be due to conduction of a supraventricular impulse, alternating along the anterior and posterior fascicles (122). However, His bundle studies (123-126) have shown that in most cases, biventricular tachycardia origi-

Figure 15. Atrioventricular node tachycardia with alternans of the QRS complex and RP and RR intervals. For explanation, see text.



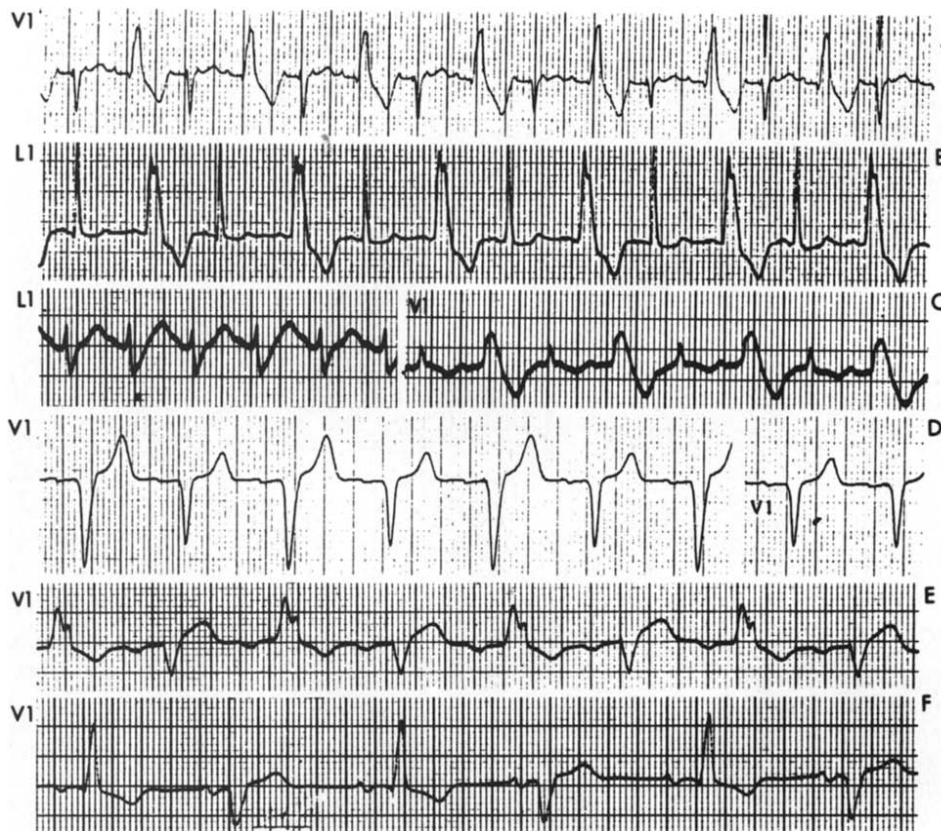


Figure 16. Different manifestations of conduction alternans involving structures distal to His bundle: right bundle branch block and normal (A), left bundle branch block and normal (B), complete and incomplete right bundle branch block (C), complete and incomplete left bundle branch block (D), right bundle branch block and left bundle branch block (E) and right bundle branch block, left bundle branch block and PR interval (F).

The following mechanisms have been proposed to explain the alternans of bundle branch block and normal conduction (A to D). 1) A small variation in the cycle length, not recognizable in the electrocardiogram. 2) The impulse blocked at the proximal edge of the "lesion" responsible for bundle branch block. This would allow for a longer period of recovery, with a bundle branch to bundle branch interval twice the basic RR cycle and thus the normal QRS complex. 3) Deceleration-dependent aberration. The normal QRS complex is followed by a bundle branch to bundle branch interval sufficiently long to permit deceleration-dependent bundle branch block. In the presence of bundle branch block, concealed transseptal activation foreshortens the bundle branch to bundle branch interval. The sinus impulse depolarizes the bundle branch at a more negative potential, resulting in normal conduction with a normal QRS complex. 4) Supernormal conduction in the bundle branch.

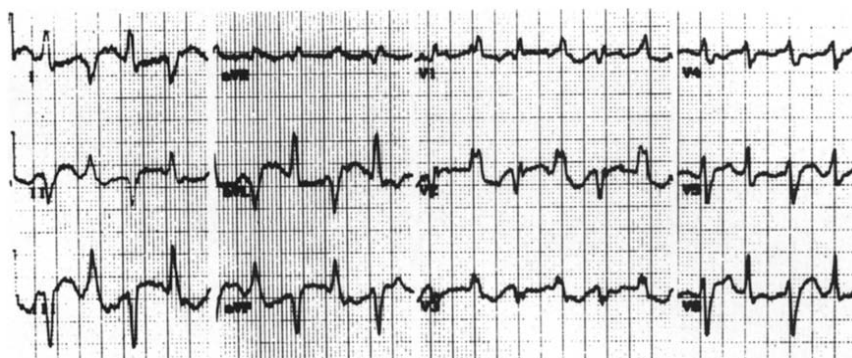
ates in the left bundle branch and conduction alternates along the anterior and posterior fascicles.

Subtle changes in QRS duration or amplitude, or both, without definite changes in the QRS axis or configuration have been observed frequently in the presence of ectopic supraventricular tachycardia with normal QRS duration. In a study (127) of a large number of patients with spontaneous or induced supraventricular tachycardia with a narrow QRS complex, QRS alternans was observed in 22% of the patients and in >90% of instances was associated with AV recipro-

In the presence of bundle branch block and delayed concealed transseptal activation of the bundle branch, the recovery curve shifts to the right, the sinus impulse fortuitously reaching the bundle branch during the supernormal period of bundle branch recovery, resulting in normal bundle branch conduction. With the normal QRS complex, the recovery curve of the bundle branch shifts to the left, the impulse falls during the time-dependent refractory period of the bundle branch and bundle branch block results. As long as the sinus rate, transseptal conduction time and onset of recovery remain constant, the alternation of bundle branch block may persist. As best can be determined in E, the PR intervals are equal, whether the conduction is by way of right or left bundle branch block. The possible mechanism is alternating transseptal conduction causing alternate change of the respective bundle to bundle interval, allowing for alternation of conduction during the supernormal periods of right and left bundle branch block. Conduction in F can be explained by alternate conduction by the right and left bundle branches with normal conduction in the right and delayed conduction in the left bundle branch. The latter would result in alternans of the PR interval.

cating tachycardia with retrograde conduction along an accessory pathway (Fig. 18). Other studies (128) tend to support these findings. However, Morady et al. (129) showed that during rapid pacing, alternans is primarily determined by the heart rate of tachycardia, independent of the mechanism. It has been suggested that both alternans during narrow QRS tachycardia and alternans of the wide QRS complex occurring occasionally during ventricular tachycardia (130) (Fig. 19) probably reflect changes in the refractoriness of the peripheral Purkinje system or ventric-

Figure 17. Atrial flutter at a rate of 300 beats/min and bidirectional ventricular tachycardia at a rate of approximately 150 beats/min with alternating right bundle branch block and left anterior fascicular block configurations.



ular myocardium. In support of this hypothesis is an observation of alternating QRS axis during ventricular pacing from a single site, illustrated in Figures 16 to 26 in the study by Cohen and Singer (131). Changes in excitability also may be responsible for alternans. An example is alternans of pacemaker spike amplitude (132,133), which may result from pacemaker generator malfunction (132).

Atrioventricular accessory pathways. Alternans of conduction has been recorded between an accessory pathway and AV node pathway (Fig. 20, bottom) between two separate accessory pathways and within a single accessory pathway (Fig. 20, top) (113).

Alternans Associated With Myocardial Ischemia

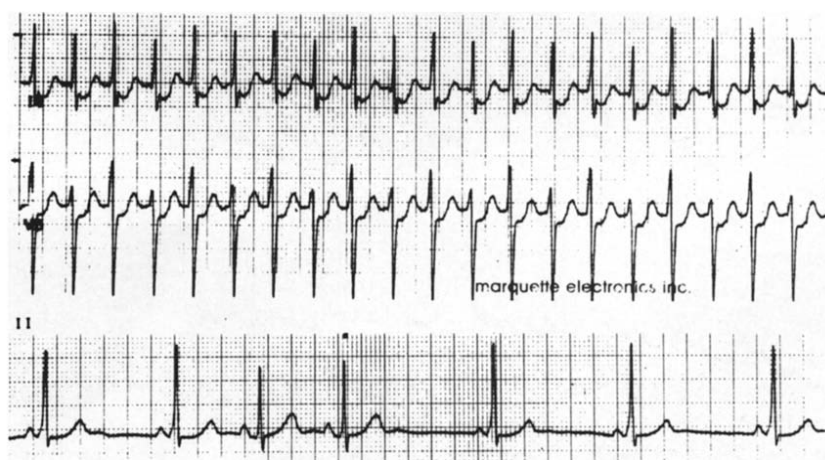
Alternans in the presence of myocardial ischemia requires special consideration because in addition to previously discussed mechanisms of mechanical (134-140) and electrical (74) alternans, myocardial ischemia may create specific types of electrical alternans resulting from electrophysiologic nonhomogeneities within the ischemic myocardium as well as between the ischemic and nonischemic myocardium.

The earliest studies of electrical alternans during experimental ischemia in animals with coronary occlusion were summarized by Hellerstein and Liebow (141). These inves-

tigators differentiated between concordant or discordant ST-T alternans, depending on whether the complexes with the larger ST-T areas were recorded simultaneously (concordant) or nonsimultaneously (discordant) in both epicardial and intracavitary leads.

The mechanism of electrical alternans at the cellular level during experimental myocardial ischemia has been studied in intact pigs and isolated pig hearts (2,142,143). Acute ischemia shortened the action potential duration and decreased action potential amplitude, velocity of depolarization and resting membrane potential. Alternans of action potential amplitude was associated with alternation of baseline and ST segment level, and alternans of upstroke velocity of the action potential was associated with alternating depolarization morphology in the extracellular signals (2). At a later stage of ischemia, postrepolarization refractoriness resulted in progressive delay of recovery that eventually caused encroachment of the stimulated complex on the next stimulus, thus producing alternans of action potential duration and refractoriness. Figure 21, from the study of Kleber et al. (2), shows ST and T wave alternans resulting from such asynchrony of local depolarization. It has been suggested that the differences in action potential amplitude and resting membrane potential during alternans create the substrate for spontaneous reexcitation, contributing to ventricular fibrillation during ischemia in the pig (2,3,143) and ventricular tachycardia or fibrillation in the dog (144,145).

Figure 18. Two upper strips, Alternans of the QRS complex in the presence of atrioventricular reentrant tachycardia. Lower strip, Pre-excitation in the first two and the last three complexes.



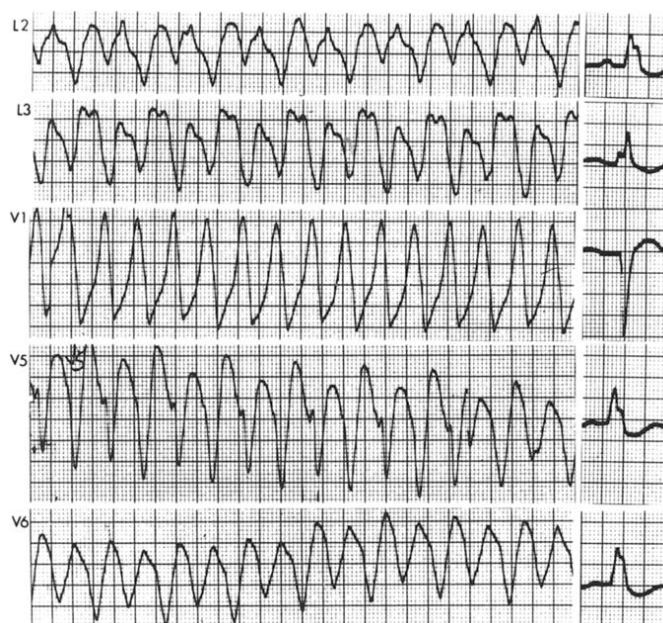


Figure 19. Ventricular tachycardia with QRS alternans possibly due to alternating intraventricular conduction time or alternating propagation pathway.

Recent studies (146) have shown that risk of ventricular fibrillation increased with increasing magnitude of ST alternans, particularly when the ST segment alternans is discordant (that is, the ST changes in the adjacent leads are out of phase) (147). Arrhythmias also have been aggravated by changes in the characteristics of ST alternans induced by ventricular premature impulses (148).

Alternans caused by asynchrony of depolarization shown in Figure 21 is not the only mechanism of ST segment alternans during acute ischemia because ST and T wave alternans have been recorded in association with alternating amplitudes and duration of monophasic action potentials

Figure 20. Wolff-Parkinson-White pattern with alternating degree of pre-excitation along an accessory pathway (top) and alternation of conduction along an accessory and atrioventricular nodal pathway (bottom).

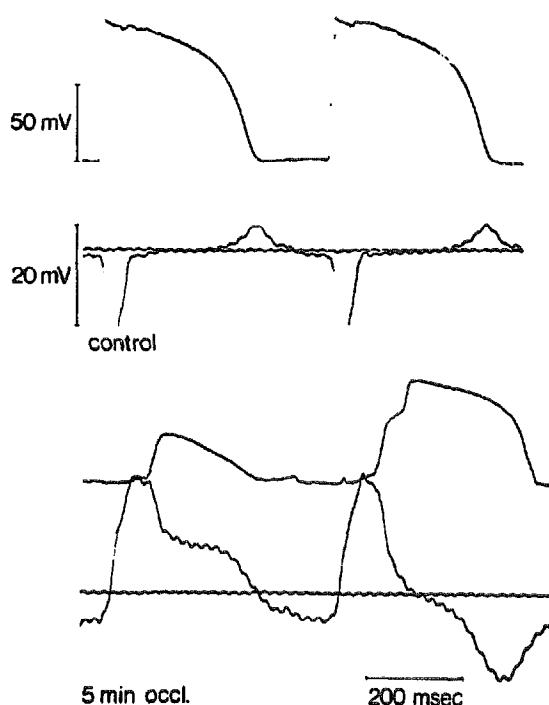
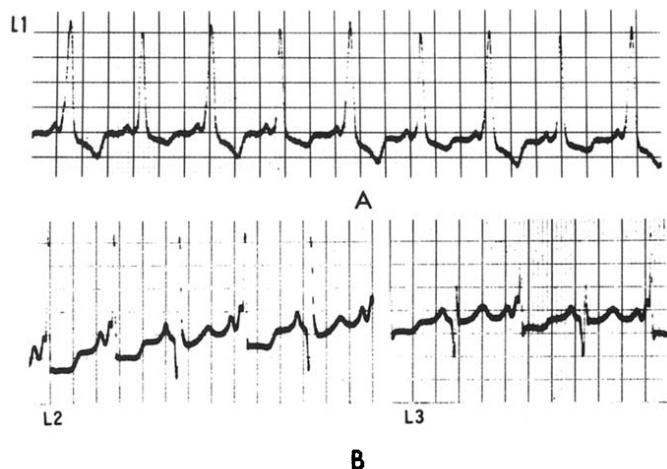
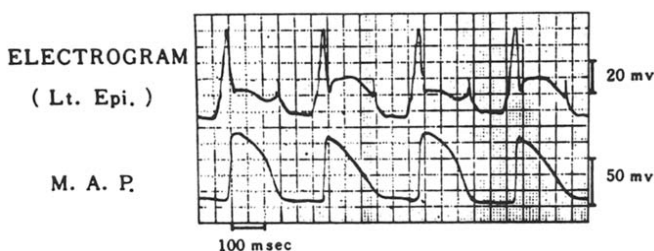


Figure 21. Transmembrane action potential and local electrogram before (top) and 5 min after (bottom) coronary occlusion (occl.) in a pig heart. Two complexes occur during alternans. Note that delayed repolarization in the ischemic area results in a negative T wave in the electrogram. Reprinted, with permission, from Kleber et al. (2).

without activation delay (Fig. 22) (144,148). ST segment alternans resulting from differences in action potential shape and levels of resting membrane potential can be produced by myocardial injury other than ischemia (for example, strong supratherapeutic transthoracic countershocks) (149).

In patients with ischemic heart disease, ST alternans usually consists of alternating levels of ST elevation in the standard or anterior precordial leads, or both, displaying an acute injury pattern with an anteriorly or inferiorly directed ST vector. Alternating levels of ST depression in these leads very seldom occur and alternating ST elevation and depres-

Figure 22. Alternans of ST segment elevation associated with alternans in monophasic action potential (M.A.P.), shape and alternans of resting potential level. Lt. Epi = left epicardial electrogram. Reprinted, with permission, from Nakashima M, Hashimoto H, Kanamaru T, Nagaya T, Hashizume M, Oishi H. Experimental studies and clinical report on the electrical alternans of ST segment during myocardial ischemia. *Jpn Heart J* 1978;19:396-408.



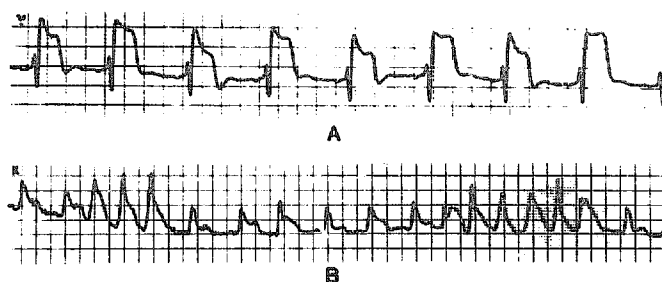


Figure 23. Alternans of the ST segment and T wave (A) in a patient with vasospastic angina pectoris associated with a brief episode of ventricular tachycardia (B). Traces A and B are reproduced at different magnifications.

sion has not been reported to our knowledge. The ST alternans is characteristically associated with vasospastic angina pectoris (Fig. 23) (150-153) but has been reported during acute myocardial infarction (154), in the presence of nonvasospastic angina pectoris (155), during exercise tests (156-158) and after subarachnoid hemorrhage (159).

Attention has been focused on the association of ST alternans during acute ischemia with the appearance or aggravation of ventricular arrhythmias, including ventricular tachycardia (Fig. 23B) and ventricular fibrillation (4). However, the frequent occurrence of such arrhythmias and sudden cardiac death during coronary spasm in the absence of ST alternans (160-165) makes it difficult to assess the specificity of this association.

Electrocardiographic Alternans in Association With Cardiac Motion

Changes in shape and amplitude of the ECG complexes have been attributed to excessive cyclic pendular and rotational cardiac motion within an enlarged pericardial sac (166-168). Such motion alters the anatomic position of cardiac regions facing the recording electrodes. Electrical alternans in patients with pericardial disease frequently suggests the presence of cardiac tamponade (Fig. 24) (168,169). Precise alternation of ECG complexes occurs

when the cardiac swinging excursions maintain two-beat periodicity (169). This is not always the case, however, and the shape or amplitude, or both, of the ECG complexes do not always fulfill the criteria of precise alternans. Some cases of electrical alternans in the presence of large pericardial effusions are accompanied by mechanical alternations (170-173).

Discussion

This survey of published information on cardiac alternans provides evidence that this phenomenon may be caused by a variety of mechanisms and may result in diverse clinical manifestations with varying diagnostic and prognostic implications.

Mechanisms. Extrapolating from *in vitro* studies, it may be assumed that mechanical alternans is caused by defects in kinetics or utilization of intracellular calcium transients responsible for a smoothly coordinated state of contraction and relaxation. In myocardial ischemia, the disturbances underlying alternans are probably precipitated by calcium overload (74). Mechanical and electrical alternans may be concurrent or dissociated from each other. Repolarization alternans in the ECG is probably caused by alternation of repolarization in the entire cardiac chamber or a large mass of cells. However, manifest alternations of conduction, refractoriness and excitability can be caused by discrete local disturbances within the conducting system or myocardium.

Certain forms of electrical alternans can be considered as physiologic manifestations of normal electrical restitution and memory. Such physiologic forms of alternans may be caused by sudden increases in heart rate or premature stimuli and are manifested by alterations of refractoriness or repolarization, or both. Such physiologic alternans is usually nonsustained because as a result of a declining memory effect, the differences between diastolic intervals gradually disappear as the action potential shortens and reaches a new steady state. However, studies *in vitro* (37) and *in vivo* (109) suggest that even in normal ventricular muscle, both me-

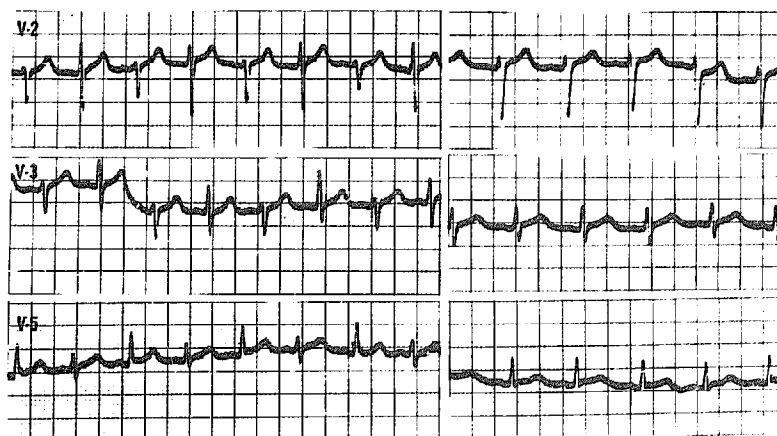


Figure 24. Alternans of the QRS complex and T wave in the presence of large pericardial effusion causing cardiac tamponade (left panel). Alternans ceases with removal of the pericardial fluid (right panel).

chanical and electrical alternans precipitated by sudden increase in heart rate may become sustained.

In addition, in vitro studies have shown that electrical alternans precipitated by factors other than a sudden increase in heart rate may be sustained at constant diastolic intervals and therefore cannot be attributed to restitution and memory effects (Fig. 7 and 8). These forms of in vitro electrical alternans are associated with mechanical alternans. It may be assumed that the alternating effects of calcium transients modulate both the developed tension and membrane currents controlling repolarization.

In vitro and clinical observations suggest that T or QT alternans is facilitated and maintained by a long duration of the action potential (or QT interval) in relation to cycle length. Alternans is precipitated by a critical shortening of the diastolic interval, which causes shortening of the following action potential and lengthening of the subsequent diastolic interval. This may be also the mechanism of bundle branch block alternans.

Clinical significance. The type of alternans that presents may provide useful diagnostic clues to specific clinical conditions. Electrical alternans in a patient with pericardial effusion, for example, suggests a large effusion with the threat of cardiac tamponade. The QRS alternans during narrow QRS tachycardia suggests AV reentry through a manifest or concealed accessory pathway. Alternating PR intervals may reveal dual AV node conduction pathways, and alternans of ST segment elevation suggests coronary spasm.

Mechanical alternans usually occurs in the failing heart. Some of the conditions precipitating cardiac failure are remediable, such as hypocalcemia, ventricular outflow obstruction and valvular regurgitation, but in many clinical cases, alternans signifies irreversibly impaired myocardial function.

The presence of alternans has been linked with the propensity for fatal ventricular arrhythmias (4,5,90). The following associations may explain these links: 1) mechanical alternans frequently occurs in patients with severely impaired ventricular function, which is a risk factor for sudden cardiac death (174); 2) repolarization alternans is frequently associated with a long QT interval or increased U wave amplitude, conditions known to precipitate torsade de pointes; and 3) ST segment alternans is associated with acute myocardial ischemia, which is an important risk factor for fatal ventricular tachyarrhythmias. In addition, in the presence of each of these high risk conditions (that is, myocardial failure, long QT interval and acute ischemia), the occurrence of alternans may facilitate or aggravate arrhythmias, particularly of the reentrant types, by increasing dispersion of repolarization and refractoriness. However, to our knowledge, the arrhythmogenic potential of alternans independent of underlying risk factors for serious life-threatening ventricular arrhythmias has not been demonstrated. Association of alternans with increased dispersion of repolarization has been documented in the setting of experimental ischemia

(144) but has not been studied in other conditions in the presence of alternans.

Conclusions. Greater insight into various mechanisms of mechanical and electrical alternans may be expected to parallel future advances in the understanding of the electro-mechanical coupling and processes controlling repolarization. At the clinical level, the mechanism and the significance of alternans can be evaluated by accurate assessment of the precipitating conditions, including the role of heart rate, rhythm disturbances and administered drugs. Since its first description as "pulsus alternans," the definition of alternans has evolved into a term encompassing multiple phenomena that are united by the label cardiac alternans but diverge widely with respect to etiology, mechanism and clinical significance.

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